REMARKS

Claims 1 – 5 and 44 - 52 are under examination in the case. Applicants remind the Examiner that the original claim was misnumbered and did not contain a claim 27. The Examiner indicated in the previous office action (Paper 8 at page 2) that claims 28-50 had been renumbered claims 27-49. Applicant had subsequently added new claims 50 to 52 so that Applicant believes that the pending claims should be 1-5 and 44-52.

Claim Objections

Claim 51 was objected to on grounds of inclusion of subject matter that was non-elected due to restriction. In response, claim 51 has been amended to limit the selected sequences to those selected in the response to the restriction.

Claim 5 was objected to as being of improper dependent form for failing to further limit the subject matter of the previous claim. In response, Applicants have amended claim 5 to recite determination of expression for genes for more than 10 genes (which is recited in claim 4). The phrase "signature gene set" has been deleted. Support for this amendment is found in the application, especially at page 16, lines 4-7, at page 20, lines 16-19, and at page 30, lines 6-13, where the determination of expression of more than 10 genes is specifically recited.

Rejection Under 35 U.S.C. §112 (First Paragraph)

Claims 1-5 and 45-52 were rejected for failing to meet the requirements of the written description provision of section 112 because of the presence of open-ended language that includes "comprising a nucleotide sequence corresponding to a gene" in claims 1 and 52. In response, Applicants have amended claim 1 to recite use of a

polynucleotide encoding the same protein as a gene having the recited activity. The specification discloses the use of a nucleotide sequence encoding the same protein (see page 8, lines 11-15 of the application) as one of the recited sequences. The claim calls for contacting the test compound with a cell that expresses a polynucleotide and that such expression could be expression of a genomic sequence, such as that present naturally in a cancerous or non-cancerous cell, or the expression of a recombinant polynucleotide, such as a cDNA that has been inserted into a cell for purposes of testing expression of the gene under condition where the test compound is or is not present. The sequences disclosed in the application were determined from RNA sequences and are thus cDNA sequences that would encode the same protein as the corresponding genomic sequences. Thus, the method of the claims should not be limited to use of the specific sequences disclosed in the application because, as described therein, the methods of the invention will commonly employ a cell, which will normally comprise the corresponding full genomic sequence, along with promoter elements and the like, as is found in nature. The sequences of the application are corresponding cDNA sequences that necessarily encode the same RNA and protein sequences as the genomic ones. In addition, the priority provisional applications for the present case, the disclosures of which have been incorporated by reference in their entireties, disclose the GenBank accession numbers for all of the SEQ ID NOs. recited in the present application (see Figure 1 in each of the priority applications).

Further, the Examiner's attention is directed to the Patent Office Guidelines on Written Description wherein it is stated that in claiming a polynucleotide sequence an Applicant is entitled to claim any sequence that, in terms of the degeneracy of the genetic code, encodes the same protein. Applicants' amendment to claim 1 accomplishes this result. Thus, it is respectfully contended that amended claim 1 meets the written description requirement.

Claim 52 was amended in a manner similar to claim 1 and therefore also meets the written description requirement.

R jecti n Under 35 U.S.C. §112 (Second Paragraph)

Claims 1-5 and 45-52 were also rejected under section 112 as being vague and indefinite for failing to particularly point out and distinctly claim the subject matter regarded by the Applicant as the invention.

Claims 1 and 52 were rejected as being vague and indefinite for use of the terms "comprising" and "corresponding." In response, Applicants reiterate that claims 1 and 52 have been amended to delete the term "corresponding to" and to use instead the phrase "encodes the same protein as" so that such purported vague and indefinite language has been modified and the claims as amended are now believed to be sufficiently clear to avoid this ground of rejection. This amendment is supported in the specification at page 8, lines 11-15.

Claims 1 and 52 were rejected as being vague and indefinite for use of the terms "increase" and "elevated" and "decreased." Applicants believe that the meaning of such terms is clear from the disclosure of the application. The concept of gene expression being increased or decreased is not new in the art. Those skilled in the art know full well how to determine if a gene's expression is decreased or increased by a particular chemical agent or not. For example, statistical analysis might dictate that the change is at least one standard deviation, which standards and yardsticks are well known to medical researchers so that it is unnecessary for Applicants to be pinned down to a specific amount, such as 2 times or 3 times the expression versus when the test compound is not present. For example, Applicants teach in the application at page 16, lines 19-28, that genes corresponding to the disclosed nucleotide sequences are increased in cancerous cells over non-cancerous cells of colon by a factor of 2 while others are decreased by a factor of 2.

In addition, for expression of genes whose expression is elevated in cancer cells over normal cells, test compounds that decrease expression of such genes by an amount

that may be within experimental error are hardly likely to be of any therapeutic value. It is clear from the application that those agents that decrease such expression the most, or that increase the expression of genes elevated in expression in normal cells versus cancerous cells, are considered the most valuable (see the application at page 32, lines 24-25, and page 18, lines 21-30).

Claims 1 and 52 were rejected as vague and indefinite for use of the phrases "cancerous cell over that in a non-cancerous cell" or "non-cancerous cell over that in a cancerous cell" in that it is not stated whether these are cells of the same tissue or organ or the same type of organism. In response, Applicants note that it is clear from the application that the disclosed sequences were identified as being elevated in colon cancer cells versus normal cells or in normal colon cells versus colon cancer cells. In addition, Applicants have amended claims 1 and 52 to recite that the comparison is for cells of the same tissue type, such as cancerous colon versus normal colon.

Claims 1 and 52 were rejected as vague and indefinite for use of the phrase "under conditions" and, in response, Applicants have amended claims 1 and 52 to recite that the cell is expressing a polynucleotide. It is believed that those of skill in the art are familiar with what is meant by a cell expressing a polynucleotide. This is further aided by the fact that expression is measured in the application by determining levels of production of RNA (see application at page 13, lines 15-16 and at page18, lines 21-30).

Claims 45-49 were rejected as vague and indefinite because earlier claim re-numbering by the Patent Office caused claim 45 to be re-numbered as claim 44. In response, Applicants have renumbered claims 46-49 to depend from claim 44 (previously numbered as claim 45) and reference to claim 45 has been deleted from these claims.

Rejection Under 35 U.S.C. §103

Initially, Applicants note that all claims were under a duty to be assigned, at the time of invention, to the inventors' common employer and the present application is so assigned.

Claims 1-5 and 45-52 were rejected under 35 U.S.C. §103(a) as being unpatentable over Robinson et al. (Pat. No. 6,232,065) in view of a number of GenBank Accession Nos., Schelegel et al. (WO 01/60860), Einat et al. (WO 00/12525) and Kinzler et al. (Pat. No. 5,702, 903).

Robinson et al. is offered as a basis of rejection on grounds that this patent discloses methods and compositions for screening factors that affect the expression patterns of individual genes or groups of genes in various disease states, including colon cancer. In response, Applicants note that the rejection concedes that the selected sequences of the application are not recited in Robinson et al..

Consequently, the Examiner offers additional citations. These include a number of GenBank Accession Nos., many of which recite sequences identical to Applicants' sequences. In response, Applicants note that the sequences disclosed in the application are not being claimed, nor are they contended to be novel. In fact, Applicants supplied GenBank Accession Nos. for all of the sequences of SEQ ID NO: 1 to 1067 disclosed in the application. These accession numbers are contained in Figure 1 of each of the provisional applications that is relied on in the present application as a priority application (the disclosures of which were incorporated by reference). One such sequence is described by Einat et al., which has 97.5% identity to SEQ ID NO: 1027 taught by Applicants but contention is made that the sequence disclosed by Einat corresponds to SEQ ID NO: 1027 or that it encodes the same protein as SEQ ID NO: 1027.

In response, Applicants contend that it is the identity of the sequences in

conjunction with their differential expression, and uses thereof, that forms a basis for the present invention. The mere fact that the sequences were previously known or that someone skilled in the art had previously disclosed use of differential expression of a gene for screening potential therapeutic agents in no way negatives patentability of the present claims.

The Examiner attempts to bolster the case for obviousness by also relying on Kinzler et al., which discloses elevated gene expression in various tumors, such as those from stomach, lung and colorectal cancer, as well as the use of normal cells to establish baseline expression levels. Again, Applicants respond that there is no mention of the sequences disclosed by Applicants as being involved in the cancerous process. The Examiner's argument is similar to one contending that because one artisan discloses a number of different anticancer drugs while another discloses that anticancer drugs have therapeutic value, it renders obvious an applicant's disclosure of a different set of anticancer drugs. The sequences and genes disclosed by Applicants herein were not previously known as being involved in the cancerous process. In addition, the Applicants' claims relate to screening agents that modulate the expression of **more than one** such gene. Thus, the Examiner's reliance on the disclosure of Kinzler et al., which is directed to one of the disclosed sequences, is unavailing because Applicants' claims are directed to screens involving more than one gene.

At best, Kinzler et al. and Robinson et al. merely tell those in the art to go out and look for genes and gene families. However, they do not render obvious the Applicant's claimed method as it involves specific sequences found by the Applicant.

The Examiner also cites Schlegel et al. as disclosing novel markers that are differentially expressed in cancer cells compared to normal cells, including a sequence (designated ABV29346) that matches SEQ ID NO; 462. In response, Applicants note that claim 1 recites comparison of gene expression up-regulated in cancer cells versus normal cells as well as gene expression up-regulated in normal cells versus cancer cells. In

addition, Applicants note that Schlegel et al. is a reference as of its publication date of 23 August 2001 (since it does not designate the U.S. – see cover page of the published application) whereas Applicants disclose SEQ ID NO: 462 as GenBank Accession No. N54841.1 (as well as other sequences with their GenBank numbers) in a provisional application, on which the present application claims priority, filed 5 June 2001 (prior to publication of Schlegel). Thus, Schlegel should not be available as a reference against the present application.

The Examiner again cites the Einat et al. publication (WO 00/12525), which discloses a sequence (AAZ51562) 97.%% identical to SEQ ID NO: 1027, and other genes differentially expressed in hypoxia and that play a role in tumors. In response, Applicants reiterate that claim 1, and claims dependent therefrom, are directed to combinations of the disclosed genes, which combinations are necessarily different from Einat et al. (even if SEQ ID NO: 7 of Einat encoded the same protein as SEQ ID NO: 1027 of the application, because the other genes are different, claims limited to the genes disclosed by Applicants should be patentable. In addition, Einat discloses genes associated with hypoxia-regulated activities (see page 2, line 25) and shows up-regulated expression following hypoxia (at page 46, lines 25-27). In short, Einat describes identification of his disclosed genes by differential response to hypoxia conditions (see page 34, lines 12-20) and not as being differentially expressed in cancer as is recited for claim 1 and the claims dependent therefrom. While Einat indicates that complex stresses due to hypoxia may play a role in neoangiogenesis seen in tumor growth, he does not suggest any study of differential expression where the determinant is cancerous growth per se. In addition, Einat in no way suggests that an important factor is also elevated expression in normal cells versus cancerous cells, so that one would be screening for agents that elevate the expression of such genes in cancerous cells rather than decreasing it. In view of the foregoing, Applicants contend that Einat is not a reference.

The Examiner further relies on Robinson et al.l as teaching the monitoring of gene expression profiles resulting from cellular and physiological changes that can then be

characterized for individual genes or groups of genes. Robinson further states that the invention can be used to screen drug compounds that affect biological samples and that human cancer is a result of genetic changes that result in alterations in the profile of expressed genes. The Examiner suggests that this method could be applied by combining the sequences of Einat and Schlegel, which are similar to two of Applicants' sequences, to find compounds that alter the differential expression between cancerous and non-cancerous cells.

In response, Applicants first reiterate their argument regarding the non-availability of Schlegel as a reference. In addition, Applicants note that these references, if combined, do not achieve the invention of the application. The Applicants concede that all of their disclosed sequences were already known in the art but not as being up-regulated in cancerous versus non-cancerous cells or vice versa. The Examiner cites accession numbers and references for sequences with high similarity to the 10 sequences previously selected by Applicant for examination but only Schlegel intimates and relation between his sequence and cancer. In addition, Applicants have amended claim 1 to recite that each polynucleotide encodes the same protein as the gene elevated in cancer or normal cells.

Furthermore, claim 50 has been amended to recite that at least one gene is elevated in cancer versus normal cells of the same tissue type and at least one gene is elevated in normal versus cancer cells of the same tissue type.

None of the references appear to recite use of genes elevated in normal cells as opposed to cancer cells although this is within the scope of claim 1 and is specifically required by claim 50. For example, Kinzler et al. uses non-cancerous cells to develop a baseline for elevated gene expression in cancerous cells but does not assess elevated production in normal cells versus cancerous cells (see Kinzler et al. at column 5, lines 60-67). In fact, several of the gene sequences provided by Applicant in the selected 10 sequences are elevated in normal over cancerous cells (for example, SEQ ID NO: 16, 87

and 651 are elevated in normal cells versus cancer cells of colon).

Additional Claim Amendments

In addition, claim 2 has been amended to recite determination of at least 3 said genes of claim 1. This amendment is supported throughout the application, especially at page 13, lines 20-22, and at page 16, lines 4-7. This amendment was made necessary by the fact that previously amended claim 1 already recites determination of more than 1 gene.

Further, claim 50 was amended to recite the method of claim 1 wherein at least one gene is a gene elevated in cancer and not in normal cells and at least one gene is elevated in normal cells and not in cancer cells. This amplifies original claim 50, where one gene was increased due to the test agent and one gene was decreased.

The Commissioner is authorized to charge payment of any additional filing fees required under 37 CFR 1.16 associated with this communication or credit any overpayment to Deposit Account No. 03-0678.

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